REMARKS

Claims 37-56 and 74-78 are pending and stand rejected, and claims 57-73 stand withdrawn. Claims 37 and 74 are amended herein to incorporate the language of claims 38, 48, and 50-55, which are cancelled herein without prejudice. Claims 40, 41, and 49 also are cancelled herein without prejudice. In addition, claim 39 is amended to remove the word "reactive," and claim 56 is amended to depend from claim 37. No new matter is added by these amendments.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 37, 39, 42-49, 56, and 74-78.

Foreign Priority

The Examiner stated that the present application claims priority from PCT/EP03/102084 and German application No. 10209822.0, both of which are in German. The Examiner further noted that no translation of the documents into English has been provided. Applicants are working to obtain the translations.

Rejection under 35 U.S.C. § 112

The Examiner rejected claims 37-56 and 74-78 under 35 U.S.C. § 112, second paragraph, alleging that they are indefinite. According to the Examiner, the term "low" in the phrase "low molecular weight substance" in claims 37, 39-42, 48, 74 and 76 is a relative term that renders the claims indefinite. The Examiner further asserted that the term "low" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants respectfully disagree. As set forth in Applicants' comments regarding the Adamson publication in the response filed on August 11, 2009, Applicants' specification discloses that the phrase "low molecular weight substance" includes peptides of up to about 50 amino acids. *See*, page 13, lines 10-12. One of skill in the art would appreciate that given an average molecular weight of 135 Daltons per amino acid residue, a peptide containing 50 amino acids would have a molecular weight of about 6750 Daltons, or 6.75 kDa. Thus, given the

teachings of Applicants' specification, the term "low" in "low molecular weight substance" is clear.

Nevertheless, to further prosecution, Applicants have amended claims 37 and 74 to recite that the low molecular weight substance is an active pharmaceutical ingredient, and that the active pharmaceutical ingredient is selected from a particular group of recited compounds. Thus, those of skill in the art would be reasonably apprised of the scope of the recited conjugates, and the present claims are clear and definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37, 39, 42-49, 56, and 74-78 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 37, 40, 41, 45-48, 50, 74, 77 and 78 under 35 U.S.C. § 102(b), alleging that they are anticipated by U.S. Patent No. 6,083,909 ("Sommermeyer"). In particular, the Examiner alleged that Sommermeyer discloses a hemoglobin-HES conjugate in which the hemoglobin and the HES are linked to one another selectively via amide bonds between free amino groups of the hemoglobin and the reducing end group of the HES, which is present in oxidized form, "which anticipates the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance." Office Action at page 4.

Applicants respectfully disagree. Sommermeyer did not anticipate the previous claims. For example, the claims require the HAS to be conjugated to a low molecular weight substance. Again, according to Applicants' specification at page 13, lines 10-12, the phrase "low molecular weight substance" includes peptides of up to about 50 amino acids. Given an average molecular weight of 135 Daltons per amino acid residue, a peptide containing 50 amino acids would have a molecular weight of about 6.75 kDa. In contrast, the hemoglobin that is conjugated to HES as described by Sommermeyer has a molecular weight of 64 kDa (see, column 1, lines 31-33). Hemoglobin therefore has a molecular weight that is about 10-fold greater than that described in Applicants' specification as "low molecular weight." Thus, hemoglobin clearly cannot be considered a "low molecular weight substance." Further, Sommermeyer fails to disclose conjugation of HES to any compound other than hemoglobin, low molecular weight or otherwise. As such, the previous claims were novel over Sommermeyer.

Nevertheless, to further prosecution, Applicants have amended claims 37 and 74 to include the language of previous claims 38 and 50-55, which are not included in the present rejection under 35 U.S.C. § 102(b). As such, Applicants submit that this rejection is moot.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 37-56 and 74-78 under 35 U.S.C. § 103(a), alleging that they are unpatentable over Sommermeyer in view of Canadian Publication No. 2233725 ("Adamson") or EP Publication No. 0331471 ("Larsen," referred to by the Examiner as "Harboe") or EP Publication No. 019403 ("Berger"). According to the Examiner, the instantly claimed conjugates differ from the conjugate of Sommermeyer by reciting a linker molecule between the HAS and to the low molecular weight substance, by reciting specific low molecular weight substances that are not disclosed by Sommermeyer, and by reciting a HAS molecule that has a molecular weight not disclosed in the Sommermeyer. The Examiner also alleged, however, the following:

- That Adamson discloses conjugates prepared by reacting hemoglobin with oxidized HES and then allowing the resultant conjugate to degrade to a lower molecular weight product after conjugation, embracing the instantly claimed conjugate of HAS and a low molecular weight substance.

- That Larsen discloses anti-inflammatory prodrugs of formula PS-O-A-(CH_2)n-B-D, where PS-OH can be HES with a MW of 40-5,000 kDa, A is CO or a direct bond, n is 0 to 14, B is O, CO, NR or a direct bond, R is H or a lower alkyl, D is R1CO or R2O, and R1COOH and R2OH are anti-inflammatory agents, such that Larsen embraces the instantly claimed conjugates.

- That Berger discloses a HAS drug that can be used in a composition for controlled release administration of biologically active compounds to animals, that bonding of active compounds to HAS can be a direct reaction, and that if the active component has a carboxylic acid functional group it can react directly or indirectly with a hydroxyl group on the HAS (e.g., as shown in Scheme I to Scheme III on page 6 of Berger), which

embraces the description of the bonding of HAS to a low molecular weight substance as recited in the instant claims.

The Examiner further alleged that it would have been obvious to one of ordinary skill in the art to incorporate into a "HAS-low molecular weight substance" conjugate of Sommermeyer a HAS comprising a specific linker, a HAS having a specific molecular weight, and a specific type of low molecular weight substance in view of the knowledge in the art, as evidenced by Adamson, Larsen, and Berger.

Applicants respectfully disagree. Without acquiescing to the Examiner's rejections and to further prosecution, claims 37 and 74 are amended herein to recite that HAS is coupled to one of a particular list of low molecular weight substances, either directly via the terminal aldehyde group of the HAS, or via a linker molecule coupled to the terminal aldehyde. No matter which coupling alternative is used, the coupling always occurs via the terminal aldehyde group of the HAS. Thus, the conjugates recited in the present claims contain HAS that has not undergone oxidation prior to being coupled to the linker or the low molecular weight substance.

Sommermeyer teaches hemoglobin-HES conjugates that are formed by coupling HES at its oxidized reducing end (i.e., with the terminal aldehyde group oxidized to a carboxyl group) to an amino group of the hemoglobin. This coupling leads to an amide bond between HES and hemoglobin. According to the teachings of Sommermeyer, it is absolutely necessary to pre-treat the HES by oxidation before it is coupled to hemoglobin in order to achieve a selective conjugation; Sommermeyer contains no teaching or suggestion to use HES in its non-oxidized state. Sommermeyer also is completely silent with regard to conjugates that contain HES coupled to a bifunctional linker compound at any location, much less at the reducing end. Further, Sommermeyer does not teach or suggest coupling HES to any compound other than hemoglobin, and thus Sommermeyer does not suggest coupling HES to any of the compounds listed in the present claims.

Neither Adamson nor Larsen nor Berger remedies the deficiencies of Sommermeyer. Adamson discloses hemoglobin-based oxygen carriers in which hemoglobin is conjugated to a polysaccharide such as HES. Like Sommermeyer, Adamson teaches that the HES is oxidized prior to conjugation, although Adamson's oxidation is disclosed to lead to a polysaccharide in

which "at least a portion of the glucose monomeric units are oxidized to present aldehyde groups." *See*, page 3, lines 31-35. Adamson's coupling therefore is non-selective. Adamson also contains no teaching or suggestion with regard to conjugates in which HES is coupled to hemoglobin via a bifunctional linker compound, and no suggestion that HES should be linked to any compound other than hemoglobin, much less one of the low molecular weight substances recited in the present claims. For at least these reasons, even if a person of ordinary skill in the art at the time of Applicants' priority date had combined Sommermeyer with Adamson – although such an assumption must be based on an *ex post facto* analysis of the prior art since Adamson clearly contradicts Sommermeyer by teaching non-selective coupling rather than selective coupling via the reducing end of HES – they would not have arrived at the subject matter recited in present claims 37 and 74.

The same is true for the alleged combination of Sommermeyer with Larsen. As in the case of Adamson, Larsen teaches the preparation of conjugates based on a non-selective strategy. In particular, Larsen teaches coupling anti-inflammatory drugs to the hydroxyl groups of a polysaccharide such as HES, which is contrary to coupling through the oxidized reducing end as disclosed in Sommermeyer. The polysaccharide hydroxyl groups are reacted with a carboxy group of a drug, leading to ester bridges between the polysaccharide and the drug. Thus Larsen, like Adamson, clearly contradicts Sommermeyer by teaching non-selective coupling rather than selective coupling via the reducing end of HES. Even if a person of ordinary skill had combined Sommermeyer with Larsen, even together with Adamson, they would not have arrived at a conjugate in which HAS is selectively coupled at a well-defined group (i.e., the terminal aldehyde) to a low molecular weight compound, wherein the HAS was not oxidized prior to coupling.

Berger also fails to remedy the deficiencies of Sommermeyer. Berger exclusively teaches non-selective coupling of HES with further compounds, either via ring-opening oxidation of monomer moieties in the starch molecule or via hydroxyl groups found somewhere in the molecule but not at a pre-defined reaction site. Thus Berger, like Larsen and Adamson, contradicts Sommermeyer by teaching non-selective coupling rather than selective coupling via the reducing end of HES. Even if one of ordinary skill in the art had combined Sommermeyer with Berger, with or without Adamson and Larsen, they would not have been prompted to make

a conjugate containing non-oxidized HAS coupled via its terminal aldehyde to a low molecular weight substance, as recited in the present claims.

For at least the above reasons, a person of ordinary skill in the art at the time of Applicants' priority date, reading the four references cited by the Examiner, would not have been prompted to combine their teachings. This is particularly true given that Adamson, Larsen, and Berger each clearly contradict Sommermeyer in teaching exclusively non-selective coupling strategies. For at least the reasons presented herein, the present claims are patentable over the cited combinations of references. Applicants respectfully request withdrawal of the rejection of claims 37, 39, 42-49, 56, and 74-78 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 37, 39, 42-49, 56, and 74-78 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $1110 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: May 3, 2010

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